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Molecular Mechanics (MM4) Calculations on [3.3]- and [4.4]Orthoparacyclophanes[†]

Kazuhisa Sakakibara,*[,‡] Keisuke Naka,[‡] Yoshitaka Yamaguchi,[‡] Masatoshi Asami,[‡]
Kuo-Hsiang Chen,[§] Jenn-Huei Lii,[§] and Norman L. Allinger[§]

Department of Applied Chemistry, Yokohama National University, 79-5 Tokoiwadai, Hodogaya-ku,
Yokohama 240-8501, Japan, and Department of Chemistry, University of Georgia,
Athens, Georgia 30602-3556

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Conformational analyses in the gas phase and the prediction of the crystal structures of 5-carboxy[3.3]orthoparacyclophane (**1**) and 6-bromo[4.4]orthoparacyclophane (**2**) were carried out by using the MM4 force field, and the calculated structures were compared with those determined by X-ray crystallographic experiments. The experimental crystal structure of 5-carboxy[3.3]orthoparacyclophane (**1**) takes on a parallel conformation where the two benzene rings have a parallel orientation, while the crystal structure of 6-bromo[4.4]orthoparacyclophane (**2**) is one with quasi-perpendicular conformation where one benzene ring tilts about 60° against the other benzene plane. The MM4 conformational analyses in the gas phase based on the calculated Gibbs free energies of the conformers have shown that the MM4 force field reproduces the experimentally determined crystal structures of the two orthoparacyclophanes (**1** (parallel) and **2** (quasi-perpendicular)) as the dominant conformers. With regard to the crystal structures, the unit cell parameters (a, b, c, α, β, γ) optimized by using the intermolecular potential energies developed for the MM4 force field agreed very well with experimental ones. The essential factors which govern the stable conformations (parallel or perpendicular) of the orthoparacyclophanes were also examined on the basis of the calculated results by the MM4 (force field) and DFT (molecular orbital) methods.

Introduction

Cyclophanes[1] are compounds having a benzenoid ring that is disubstituted in the ortho, meta, or para positions by a closed chain of carbon atoms, usually methylene groups. If the carbon chain is interrupted by other benzenoid rings similarly disubstituted, the synthesized cyclophanes ([*m.n*]cyclophanes) may have unique structures (stable conformations) depending on the methylene chain length and the substitution pattern of the benzenoid rings. Whether two benzene rings are held face to face by methylene bridges, or a benzene ring orients perpendicularly against the other benzene ring, is an interesting research topic and should be studied carefully. As the [*m.n*]cyclophanes are conformationally flexible due to the relatively free rotation of the methylene units, it is rather difficult for theoretical methods to predict the conformational equilibria correctly in the gas phase. Though molecular mechanics is a practical and efficient research tool for the purpose of conformational analyses of this kind of [*m.n*]cyclophane system, the accurate evaluation of the interatomic potential functions exerted in the molecules is prerequisite. The crystal structures and the conformational equilibria can be predicted correctly only when accurate intramolecular and intermolecular interaction potentials have been settled in the force field. The MM4[2] force field is an improved force field further developed from the MM3[3] force field, which enables us to reproduce an accuracy and reliability comparable to high level ab initio calculations including electron correlation and/or elaborate experiments. As we succeeded in the syntheses[4] of 5-carboxy[3.3]orthoparacyclophane (**1**) and 6-bromo[4.4]orthoparacyclophane (**2**), and in determining the crystal structures of these molecules by X-ray crystallographic analysis, it is a challenging opportunity to investigate whether the MM4 and/or MM3 force fields can evaluate the structures of these two orthoparacyclophanes correctly in the gas phase and in the crystal.

In this paper we report the X-ray crystallographic structures of 5-carboxy[3.3]orthoparacyclophane (**1**) and 6-bromo[4.4]orthoparacyclophane (**2**). These crystal structures could be reproduced well by only the MM4 force field. The stable structures calculated from the conformational analyses of these orthoparacyclophanes in the gas phase were compared with those of the crystal structures, and the principal factors for stabilizing the dominant conformers in the crystal and in the gas phase were studied.

Structures of 5-Carboxy[3.3]orthoparacyclophane (1) and 6-Bromo[4.4]orthoparacyclophane (2) in the Crystal

The structural investigations of the orthoparacyclophanes have been carried out previously by X-ray crystallographic experiments, NMR, or semiempirical molecular orbital calculations (Scheme 1). Tobe et al. have synthesized [2.2]orthoparacyclophane (**3**) and 5-methoxycarbonyl[2.2]orthoparacyclophane (**4**), and their stable conformations were found to be one where two benzene rings are parallel[5] by measuring NMR spectra in solution, and by semiempirical molecular orbital AM1 calculations. The conformational behavior of 2,11-dithia[3.3]orthoparacyclophane (**5**) in solution and in the solid state was studied by Hopf et al.,[6] and the parallel conformation with regard to the two benzene rings was found to be the dominant one. On the contrary, the molecular structure of 2,13-dithia[4.4]ortho-

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[‡] Yokohama National University.
[§] University of Georgia.

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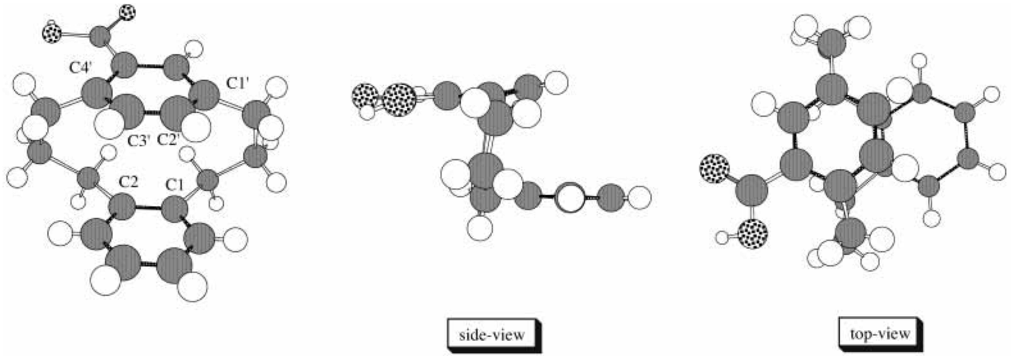
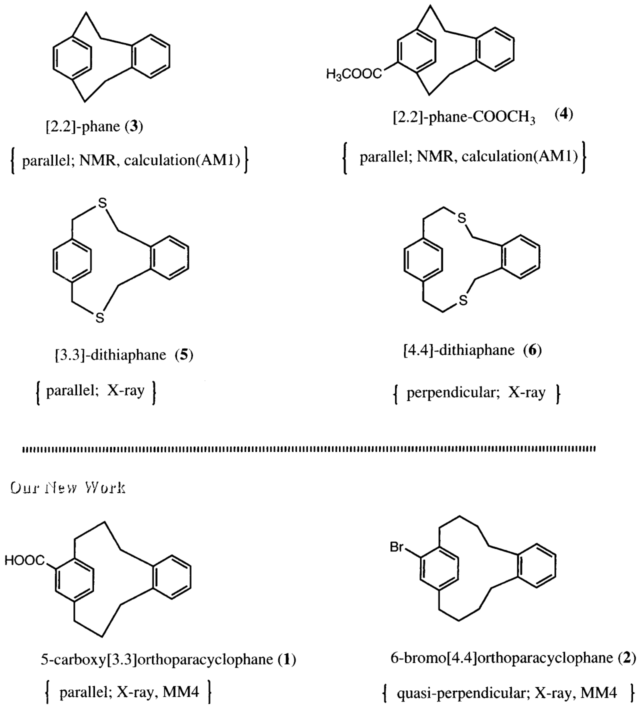


Figure 1. Crystal structure of 5-carboxy[3.3]orthoparacyclophane (**1**).

SCHEME 1: Reported Molecular Structures of Orthoparacyclophanes



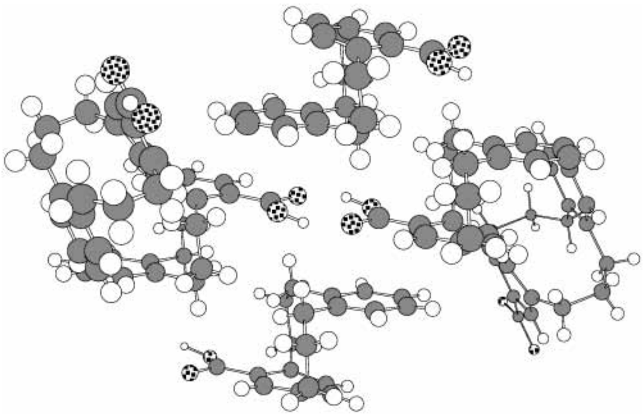


Figure 2. Intermolecular hydrogen bonds between the OH proton and the carbonyl oxygen atom in the crystal cage of 5-carboxy[3.3]-orthoparacyclophane (**1**).

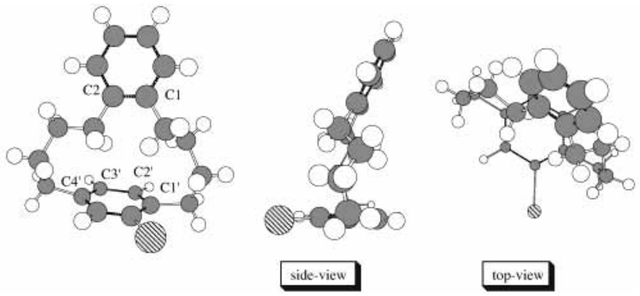


Figure 3. Crystal structure of 6-bromo[4.4]orthoparacyclophane (**2**).

paracyclophane (**6**) was reported to be the perpendicular one by Asami et al.,[7] from X-ray crystallographic experiments.

The preferred conformation of the [*m.n*]orthoparacyclophane molecules changes depending on the length of the methylene chains connecting the two benzene rings. It seems plausible to think that a smaller chain length (i.e., in the case where the number of heavy atoms comprising the chain (*N*) is two or three) favors the parallel conformation. It is important to note that a benzene ring is longer (or wider) than it is thick. Hence if you try to press benzene rings as close together as possible, they will be parallel. Therefore, if the rings are connected by short chains, they try to come together in a parallel fashion from van der Waals forces. The rings themselves, without any effect from the side chains, would prefer to be perpendicular (as in the benzene dimer). If the side chains will allow it, that is the geometry we expect to find. Thus, for the case at hand, the short chains should lead to more parallel structures and the longer chains to more perpendicular structures.

The parallel structures will have the most favorable van der Waals interaction, if they are far enough apart, when the stacking is like "pancakes", that is, directly above one another. However, that is bad for the electrostatics, because the dipoles are directly one above the other. Thus, the net effect is that one ring will like to slide parallel to the other if it can, because that tends to put the positive hydrogens over negative carbons, rather than put one positive hydrogen over another one.

As shown in the experimental results of the [2.2]orthoparacyclophanes (**3** and **4**)[5], these smaller chain lengths lead to a strained structure. What is the principal driving force leading to the parallel conformation in the [*m.n*]orthoparacyclophane molecules? Does the crystal structure correspond to the global minimum energy conformation in the gas phase? MM4 force field calculations in conjunction with the X-ray crystallographic experiments on the orthoparacyclophanes can be utilized to obtain meaningful knowledge to answer this intriguing scientific question.

The experimentally determined crystal structures of 5-carboxy-[3.3]orthoparacyclophane (**1**) and 6-bromo[4.4]orthoparacyclophane (**2**) are shown in Figure 1, Figure 2 (which shows intermolecular hydrogen bonds in **1**), and Figure 3, respectively. In addition to the perspective view, the side and the top views of the molecule are also shown to make clear the relative conformations of the two benzene rings. The crystal data and

TABLE 1: Crystal Data and the Unit Cell Parameters of 5-Carboxy[3.3]orthoparacyclophane (1) and 6-Bromo[4.4]orthoparacyclophane (2)

	5-carboxy[3.3]orthoparacyclophane (**1**)	6-bromo[4.4]orthoparacyclophane (**2**)
chemical formula	$C_{19}H_{20}O_2$	$C_{20}H_{23}Br$
molecular weight	280.37	340.31
crystal description	plate	prismatic
crystal color	colorless	colorless
crystal system	monoclinic	orthorhombic
space group	*P*21/*n* (No. 14)[a]	*Pbca* (No. 61)[a]
a (Å)	8.158(4)	16.915(5)
b (Å)	22.940(7)	19.842(4)
c (Å)	8.542(3)	10.073(3)
α (deg)	90	90
β (deg)	112.82(3)	90
γ (deg)	90	90
cell volume *V* (Å^3)	1473(1)	3380(1)
Z	4	8
D_{calcd} (g/cm^3)	1.264	1.349
temp (K)	296(1)	296(1)
reflns measd	4610	3133
independent reflns	4224	2754
R_1 ($I > 2.0\sigma(I)$)	0.094	0.056
R_w (all data)	0.296	0.195
GOF[b]	1.47	1.17

[a] The space group number registered in the International Table for the space group. [b] Goodness of fit indicator.

the unit cell parameters (*a*, *b*, *c*, α, *β*, *γ*) at room temperature are compiled in Table 1.

As can be recognized easily from Figure 1, the two benzene rings of 5-carboxy[3.3]orthoparacyclophane (**1**) are oriented in parallel (the angle formed by the two rings is 7°). One C−C bond (C1−C2) in the ortho-bridged benzene ring is located so as to be superimposable with the other C−C bond (C2′−C3′) in the para-bridged benzene ring. The nonbonded atomic distances between thus vertically superimposed carbon atoms are 3.149 Å for C1···C2′ and 3.121 Å for C2···C3′, respectively. These nonbonded atomic distance values are considerably smaller than the sum of the van der Waals radii[8] of the benzene rings (3.54 Å). The closer contact of them suggests that some special interaction may exist between the two aromatic rings in the case of the smaller methylene chain lengths of the orthoparacyclophanes such as **1**. This topic is discussed in detail later. The deformation of the benzene rings from planarity is noteworthy. The out-of plane deformation of the para-bridged benzene ring (−4.0° to + 3.8°) is larger than that of the ortho-bridged benzene ring (−0.8° to +0.5°). As the deformation of the benzene ring appears to be inevitable to form the [*m.n*]-cyclophanes, the molecule may relax the steric strain mainly by deforming the para-bridged benzene ring. The larger deformation of the para-bridged benzene ring has also been predicted with [2.2]orthoparacyclophanes from the AM1 optimized geometries.[5] The other noteworthy structural feature of **1** is the conformation of the methylene chains connecting the benzene rings. The four carbon atom sequences which start from the para-bridged benzene sp^2 carbon atoms (C1′−C(sp^3)−C(sp^3)−C(sp^3) and C4′−C(sp^3)−C(sp^3)−C(sp^3)) are found to have distorted eclipsed conformations. The dihedral angles of these atom sequences are ω_1(C1′−C(sp^3)−C(sp^3)−C(sp^3)) = −11.3° and ω_2(C4′−C(sp^3)−C(sp^3)−C(sp^3)) = 18.5°, respectively. On the contrary, the corresponding four atom sequences starting from the ortho-bridged benzene sp^2 carbon atoms (C1−C(sp^3)−C(sp^3)−C(sp^3), −61.0°; C2−C(sp^3)−C(sp^3)−C(sp^3), 56.4°) are found to have the usual gauche conformations. In addition, intermolecular hydrogen bonds between the carboxyl groups are observed (Figure 2). Although the carboxyl group tends to take the usual s-cis conformation[9] where the carbonyl C═O bond eclipses the carboxylic O−H bond, the carboxylic hydrogen atom was forced to deform from the plane formed by the para-bridged benzene and carbonyl group owing to the geometric requirements to make intermolecular hydrogen bonds possible. As shown in Figure 2, intermolecular hydrogen bonds between the −OH proton and the carbonyl oxygen atom can be recognized. The atomic distances between the oxygen atoms of the hydroxyl group and the carbonyl group were both 2.647 Å, and the nonbonded distance between the carbonyl carbon atoms in the carboxyl groups was 3.867 Å. These nonbonded distances relevant to the intermolecular hydrogen bond formation were similar to those reported in the cases of the hydrogen-bonded carboxylic acid dimer structures of formic acid, acetic acid, and propionic acid.[10]

The crystal structure of 6-bromo[4.4]orthoparacyclophane (**2**) is shown in Figure 3 to be in a quasi-perpendicular conformation where one benzene ring tilts about 60° against the other benzene plane. As reported also in the crystal structure of 2,13-dithia-[4.4]orthoparacyclophane (**6**), the longer methylene chain length seems to favor the perpendicular conformation. Though a significant deformation of the para-bridged benzene ring from planarity was also observed here, the extent of the deformation (−1.5° to + 1.4°) was smaller than that of 5-carboxy[3.3]-orthoparacyclophane (**1**) (−4.0° to + 3.8°). The smaller strain in 6-bromo[4.4]orthoparacyclophane (**2**) appears to come from the longer chain length, which affords more conformational flexibility to relax the geometric strain. The strain relief may also be recognized from the conformation of the bridging methylene chains of **2**. As studied in 5-carboxy[3.3]orthoparacyclophane (**1**), the conformations of the four carbon atom sequences starting from the para-bridged benzene sp^2 carbon atoms were investigated. The dihedral angles of ω_3(C1′−C(sp^3)−C(sp^3)−C(sp^3)) and ω_4(C4′−C(sp^3)−C(sp^3)−C(sp^3)) are −47.5° and 57.1°, respectively. These observed dihedral angles correspond to only slightly deformed gauche conformations. The corresponding four atom sequences starting from the ortho-bridged benzene sp^2 carbon atoms indicated that their dihedral angles were those corresponding to the usual anti conformation. The nonbonding atomic distances between the ortho- and para-bridged benzene rings are 4.633 Å (C1---C1′) and 4.463 Å (C2---C4′), respectively. One C−C bond (C1−C2) of the ortho-bridged benzene ring is positioned perpendicularly over the C2′−C3′ bond of the para-bridged benzene ring, as found in 5-carboxy[3.3]orthoparacyclophane (**1**). It is

TABLE 2: Conformational Analysis of 5-Carboxy[3.3]orthoparacyclophane by the MM4 Force Field

ID	conformation[a]	ΔG (kcal/mol)	population (%)	stability order	ΔE (kcal/mol)	stability order
Conf1	parallel (X-ray)	0.41	22.5	2	0.07	2
Conf2	perpendicular	1.55	3.3	8	1.43	8
Conf3		0.83	11.0	3	0.63	3
Conf4		1.49	3.6	7	1.16	4
Conf5	parallel (X-ray)	1.99	1.6	9	1.31	5
Conf6		1.39	4.3	6	1.39	7
Conf7		1.39	4.3	5	1.39	6
Conf8	parallel (X-ray)	0.00	44.7	1	0.00	1
Conf9	perpendicular	1.32	4.8	4	1.54	9

[a] Relative conformations of the two benzene rings. "X-ray" means that its conformation is similar to that of the crystal structure. Blank means that the conformation is intermediate between the parallel and perpendicular conformations.

interesting to note that the ortho-bridged benzene ring tends to be located in a position so as to avoid the van der Waals repulsion of the bulky substituents in the para-bridged benzene ring (5-carboxy group in **1** and 6-bromo group in **2**). As the orientation of the two benzene rings in **2** are not suitable for a $\pi-\pi$ interaction, the important factors which determine the conformation of **2** in the crystal are evidently the van der Waals interactions and the torsional energies along the methylene bridges connecting the benzene rings. The benzene dimer is perpendicular, so that if the side chains were long enough in these compounds, presumably a perpendicular arrangement of the benzene rings would be found. If the chains are too short, some kind of compromise must be reached, to have a minimum of energy.

Conformational Analyses of 5-Carboxy[3.3]orthoparacyclophane (1) and 6-Bromo[4.4]orthoparacyclophane (2) by MM4 Force Field Calculations

MM4 conformational analyses of 5-carboxy[3.3]orthoparacyclophane (**1**) and 6-bromo[4.4]orthoparacyclophane (**2**) were carried out by using the stochastic search program of Saunders[11] to find the stable conformers in the gas phase, and to compare the crystal structures of **1** and **2** with the corresponding stable conformations calculated by MM4. The population of the each conformer was determined from the Gibbs free energy after carrying out the MM4 vibrational analysis.

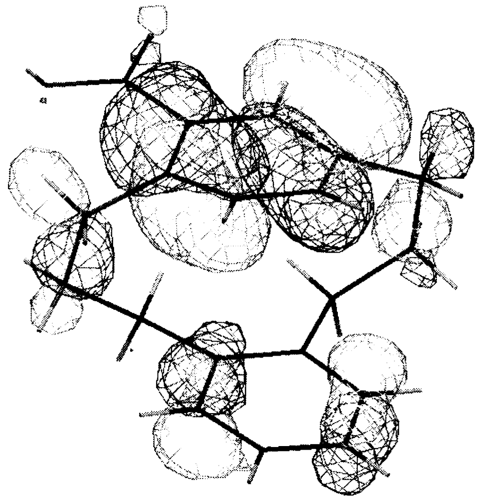
The conformational equilibrium of 5-carboxy[3.3]orthoparacyclophane (**1**) calculated by the MM4 force field (gas phase) is shown in Table 2. The Gibbs free energy for each conformer indicates that conformer **8** is the most stable (population 44.7%), and its structure with regard to the relative conformation of the two benzene rings is similar to the observed crystal structure (parallel conformation). Conformer **1** is similar to conformer **8** with a little difference in the methylene-bridge conformations, and is the second most stable (population 22.5%). On the whole, the structure of the most stable conformer (conformer **8**) is almost as the same as that of the crystal structure. Two conformers which have perpendicular conformations of the two benzene rings were also found (conformers **9** and **2**). However, their population numbers are small (conformer **9**, 4.8%; conformer **2**, 3.3%), indicating that the parallel conformation is more favorable when the number of carbon atoms comprising the methylene bridges is three. There exist also intermediate conformations between the parallel and perpendicular conformations, though their population numbers are small.

By investigating the individual energy component terms of the steric energy in the MM4 force field, we could evaluate the contributing factors which cause the parallel conformation to be more stable. Significant differences in the torsional and van der Waals energy terms in the MM4 calculations were noted between the parallel and perpendicular conformations. In the conformers taking the parallel conformation, the torsional energy is smaller by 1−2 kcal/mol than in the perpendicular conformations. The main torsional strain comes from the para-bridged benzene rings and their connecting methylene bridges. The parallel conformers tend to relieve torsional strain as much as possible by assuming gauche or anti conformations with regard to the C−C−C−C dihedral angles. However, the torsionally favorable conformations give rise to an increase in the van der Waals repulsion. Therefore, the parallel conformers have larger van der Waals energy terms by about 1 kcal/mol than the perpendicular conformers. The balance between the torsional strain and the van der Waals interaction appears to mainly determine the preferred conformations of the 5-carboxy[3.3]-orthoparacyclophane (**1**).

It may be suitable to mention here the reason the MM4 force field can perform better than the previous force field (MM3) in the structural analyses. The main things that make the MM4 results different from the MM3 results in the present case are these: van der Waals interactions, electrostatics, and, in some cases, energy cross terms. The van der Waals numbers are more carefully determined and are a small improvement over those in MM3. However, because these numbers are important and come in everywhere, they sometimes have a noticeable overall effect. Also important, the aromatic C−H bond has a small dipole moment (about 0.6 D) in MM4, and not in MM3. While the effect is small in terms of energy, it tends to make two benzene rings more stable when they are oriented in a perpendicular fashion, as opposed to a parallel fashion (where van der Waals forces dominate). The cross terms (stretch−bend, and especially torsion−bend, for example) can become rather important if a molecule is highly deformed. By comparing the energetic terms in the MM4 calculations with those of the MM3, significant energetic terms which are supposed to be responsible for the better performance of the MM4 could be recognized, though it is rather difficult to extract principal factors from the many comprising energetic terms in the force field. They were the electrostatics (the aromatic C−H bond dipole), long-range van der Waals interactions, and torsion−bend cross term (by a lesser extent). These enrgy terms in the MM4 force field did have significant amounts of numbers, and could be assumed to contribute to determining the conformations of cyclophanes appropriately.

Quantum mechanical (QM) studies also support the results derived from the MM4 calculations. The single point energy calculation of the 5-carboxy[3.3]orthoparacyclophane (**1**) at the geometry determined by the X-ray crystallographic experiment with the density functional (DFT)[12] method was carried out at the B3LYP/6-31G*[13] level by using the Gaussian 94 program.[14] As one C−C bond (C1−C2) in the ortho-bridged benzene was

HOMO (Highest Occupied Molecular Orbital)



LUMO (Lowest Unoccupied Molecular Orbital)

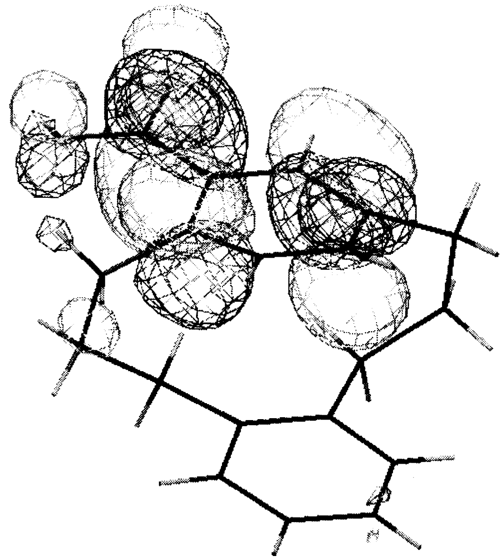


Figure 4. Frontier orbitals (HOMO and LUMO) of 5-carboxy[3.3]-orthoparacyclophane (**1**). Electron distribution was obtained by B3LYP/6-31G* DFT calculation.

located to be superimposable vertically with the other C−C bond (C2′−C3′) in the para-bridged benzene, and their nonbonded atomic distances were smaller than the sum of the van der Waals radii of the benzene rings (Figure 1), it might have been suspected that there exist attractive interactions between the two benzene rings. However, no evidence indicating any attractive interaction between the benzene rings could be found from this DFT calculation. The overlap populations between these closely located nonbonded carbon atoms of the vertically superimposed C−C bonds (C1−C2 and C2′−C3′) were negative, though their atomic distances range from 3.12 to 3.15 Å. In addition, frontier orbital interactions between the HOMO and LUMO cannot be significant, because the LUMO does not have any π-orbital component on the ortho-bridged benzene ring to interact with the HOMO as shown in Figure 4. Therefore, DFT calculations indicated that no electron delocalization between the two benzene rings occurs. It is reasonable to think that torsional strain and van der Waals interaction are the principal factors that lead to the parallel conformation being stable.

For both molecules **1** and **2**, a conformational search was carried out with MM4. One expects that for each of these molecules there will be a number of relatively stable conformations. From the search routine, the structures that had steric energies of no more than 4 kcal/mol above the lowest one found were all saved. These steric energies are a measure of the energy (as opposed to the enthalpy) of the molecule. Of course, what one really wants to find out is the structure of the conformation that has the lowest free energy. As an approximation, one often uses these steric energies in place of the free energies, sometimes with entropy corrections for symmetry. In Table 2 are given both the free energies and the energies of the various conformations found for **1**. The two most stable conformations (Conf8 and Conf1, in both energy and free energy) have parallel benzene rings, and they are much more stable than the lowest perpendicular conformation. Since the conformations all have C_1 symmetry, it is expected that their entropies will be rather similar, and not only the enthalpies, but also the free energies will tend to parallel the steric energies. This is what is found.

In Table 3 are shown the corresponding data for compound **2**. In this compound, because the structures tend to be more flexible, it might be expected that the stability orders of the energies and free energies would tend to be more different. Also, because the chains are longer, one might expect, and one finds, more conformations within the 4 kcal energy cutoff. Indeed, the conformation of **2** with the lowest steric energy is not the most stable conformation, but rather is ninth in stability order in terms of free energy. This example shows what a poor approximation it can be to use the steric energies to approximate the free enrgies. In this case the four lowest energy conformations have an X-ray or perpendicular type structure. In contrast, with compound **1**, the two most stable structures are parallel, and they are much more stable than the other structures.

In both molecules **1** and **2**, the energy is, of course, important, but the entropy appears to be of overriding importance in molecule **2**, though not in **1**, where the chains are too short to allow for very much entropy difference flexibility. It may be appropriate to mention that there exist the uncertainties of the calculated free energy. Some of the conformations, in both molecules **1** and **2**, have low frequencies (18−39 cm^{-1}), and these lead to uncertainties on the order of 0.8−1.0 kcal/mol in the free energy (a limitation of the harmonic approximation in the vibrational treatment).

The distribution of the steric strain could also be evaluated from the steric energy components of the MM4 force field, though the structural data derived from the X-ray geometries of cyclophanes **1** and **2** did show that steric strain (the out-of-plane bending deformation and the torsional strain) was relieved significantly in **2** compared with **1**. The MM4 torsional energy terms of **2** are smaller than those of **1** by about 5−10 kcal/mol because molecule **2** can take up strainless gauche or anti conformations due to the greater flexibility of the longer methylene bridge chains. As 6-bromo[4.4]orthoparacyclophane (**2**) has this conformational flexibility, many more conformations are possible. By inspecting the calculated structures carefully, subtle conformational changes with regard to the steric orientations of two benzene rings could be recognized in the stable conformations. It should be remembered that the contribution of the entropy term to the conformational equilibria is more important with the more flexible molecules such as 6-bromo-[4.4]orthoparacyclophane (**2**). On the whole, we can say that the MM4 force field appears to predict the conformational

TABLE 3: Conformational Analysis of 6-Bromo[4.4]orthoparacyclophane by the MM4 Force Field

ID	conformation[a]	ΔG (kcal/mol)	population (%)	stability order	ΔE (kcal/mol)	stability order
Conf1	perpendicular	0.41	9.3	5	1.34	9
Conf2	perpendicular	0.77	5.1	7	1.16	8
Conf3	X-ray	0.00	18.6	2	0.64	4
Conf4	X-ray	0.09	16.0	3	0.95	6
Conf5		0.16	14.2	4	1.07	7
Conf6		0.46	8.5	6	1.38	10
Conf7	quasi-parallel	1.11	2.8	9	0.00	1
Conf8	quasi-parallel	1.11	2.8	10	0.01	2
Conf9	X-ray	0.00	18.6	1	0.64	3
Conf10		0.90	4.1	8	0.81	5

[a] Relative conformations of the two benzene rings. “X-ray” means that its conformation is similar to that of the crystal structure. Blank means that the conformation is intermediate between the parallel and perpendicular conformations.

TABLE 4: Comparison of the MM4 Structures (rms Values) for 5-Carboxy[3.3]orthoparacyclophane (1) to the Experimentally Determined Crystal Structure

MM4 structures	conformation	atomic positions[b]	bond lengths (Å)	bond angles (deg)	out-of-plane angles[c] (deg)	torsional angles (deg)
crystal struct		0.129	0.035	1.99	0.87	5.4
Gas-phase[a]						
Conf1	parallel (X-ray)	0.350	0.037	2.73	1.44	18.2
Conf2	perpendicular	1.203	0.036	3.51	2.32	45.2
Conf3		0.794	0.037	3.45	1.69	30.2
Conf4		1.455	0.037	3.46	1.71	48.8
Conf5	parallel (X-ray)	0.720	0.036	2.60	1.54	48.2
Conf6		0.990	0.037	3.41	1.77	53.2
Conf7		0.990	0.037	3.41	1.77	53.2
Conf8	parallel (X-ray)	0.319	0.037	2.54	1.37	16.5
Conf9	perpendicular	1.198	0.036	3.36	2.29	44.9

[a] The conformers listed in boldface type take on a parallel conformation, while those listed in italics take on a perpendicular conformation. [b] These are the rms differences in the atomic coordinates of the heavy atoms for the whole crystals. The numbers are large, but not because the molecules are displaced slightly and twisted slightly relative to one another. [c] The benzene ring carbons relative to the mean plane.

equilibrium correctly for the orthoparacyclophane molecules **1** and **2**. The MM3 force field could not make this prediction as accurately as the MM4 force field did. With the MM3 force field, the most stable conformation of **2** was predicted to be a perpendicular one similar to the conformer **1** in Table 3, and the population of the conformers similar to the X-ray structure was reduced significantly. The inclusion of the aromatic C−H bond dipole and the induced dipole moment energy term into the MM4 force field seemed to be effective in stabilizing the X-ray structure (one benzene ring tilts about 60° against the other benzene ring). The trend in the results of these calculations might have been anticipated, since MM3 calculations yield a very stable parallel benzene dimer, while the favored dimeric structure from MM4 is perpendicular (as found experimentally). If idealized dimeric structures are prevented by constraints, as in the present case, the trends should still be in the indicated direction.

Evaluation of the Crystal Structure by the MM4 Force Field

“Are crystal structures predictable?”[15] is one of the challenging problems that many scientists have been trying to solve. Though a terse negative reply[16] to this question was given earlier, many research and development efforts[17] have continued aimed at evaluating the intermolecular interaction energies correctly in the crystal. As Dunitz[15] comments, the problem is not so much a matter of generating stable crystal structures, but rather one of selecting one or more from many almost equienergetic possibilities. Therefore, the accuracy of the force field is very important. As the MM4 force field has shown reliable results for the conformational equilibria of 5-carboxy-[3.3]orthoparacyclophane (**1**) and 6-bromo[4.4]orthoparacyclophane (**2**) with regard to the geometries and the conformational energies, it is a good opportunity to check whether the MM4 force field is accurate enough to predict the crystal structure.

As the crystal environment can be created easily on the basis of the optimized geometry calculated by the MM4 force field according to the symmetry of the space group, estimation of the crystal structure stabilities can be carried out by constructing and optimizing appropriate MM4 crystal environment models. The procedure used to calculate the unit cell parameters and the lattice energies was followed basically as reported for the crystal data for aliphatic and aromatic hydrocarbons using the MM3 force field.[3c] The process using the FORTRAN program CRSTL to optimize the crystal structure may be outlined as follows.

1. On the basis of the optimized isolated stable conformer structure from the MM4 force field, a crystal environment (ca. 1000 atoms) was generated from the experimental crystal structures, and all atoms other than the central molecule were restricted to have their atomic coordinates fixed. Then, the geometry optimization of the central molecule was carried out.
2. The next step was to minimize the unit cell constants. This was done by iteratively optimizing the crystal geometry (cell constants), with the internal coordinates of the molecules fixed, until the lattice energy minimum was found.
3. The above two processes were then repeated alternately and iteratively until the self-consistent point was located. Thus, both the lattice energy and the cell constants of the crystal, as well as the geometry of the molecule in the lattice, were determined by the MM4 force field.

The tables for comparison of the MM4 gas-phase and crystal structures are compared to the experimental crystal structures by looking at the root-mean-square (rms) values for the atomic coordinates, bond lengths, and angles. These values are shown in Table 4 (5-carboxy[3.3]orthoparacyclophane (**1**)) and in Table

TABLE 5: Comparison of the MM4 Structures (rms Values) for 6-Bromo[4.4]orthoparacyclophane (2) to the Experimentally Determined Crystal Structure

MM4 structures	conformation	atomic positions[b]	bond lengths (Å)	bond angles (deg)	out-of-plane angles[c] (deg)	torsional angles (deg)
crystal struct		0.085	0.044	1.54	0.32	2.2
Gas-phase[a]						
Conf1	perpendicular	0.496	0.052	2.01	0.54	40.0
Conf2	perpendicular	0.619	0.052	2.12	0.79	49.6
Conf3	X-ray	0.609	0.052	1.50	0.42	5.5
Conf4	X-ray	0.327	0.052	2.19	0.53	20.7
Conf5		0.847	0.052	2.28	0.69	54.5
Conf6		0.830	0.052	1.64	0.49	54.1
Conf7	quasi-parallel	0.851	0.052	1.70	0.61	57.4
Conf8	quasi-parallel	0.850	0.052	1.70	0.61	57.4
Conf9	X-ray	0.162	0.052	1.50	0.42	5.5
Conf10		0.655	0.052	1.47	0.94	42.0

[a] The conformers listed in boldface type take on a quasi-perpendicular (X-ray) conformation, while those listed in italics take on a quasi-parallel conformation. [b] These are the rms differences in the atomic coordinates of the heavy atoms for the whole crystals. The numbers are large, but not because the molecules are displaced slightly and twisted slightly relative to one another. [c] The benzene ring carbons relative to the mean plane.

TABLE 6: Unit Cell Parameters and Lattice Energies of 5-Carboxy[3.3]orthoparacyclophane (1) Calculated by MM4 Force Field and Measured by Experiment

	MM4	experiment
a (Å)	8.0405	8.158(4)
b (Å)	22.4045	22.940(7)
c (Å)	8.4313	8.542(3)
α (deg)	90.6392	90
β (deg)	111.5878	112.82(3)
γ (deg)	89.3617	90
cell volume V (Å^3)	1475.2152	1473(1)
Z	4	4
temperature (K)	298.2	296(1)
lattice energy (kcal/mol)	−23.47	

5 (6-bromo[4.4]orthoparacyclophane (**2**)). From these rms values, we can say that the MM4 estimated crystal structures are the most similar to the experimentally determined crystal structures, for both the orthoparacyclophanes (**1** and **2**), and the crystal structures are different from those predicted to be stable in the gas phase, due to the intermolecular interactions in the crystal.

The calculated unit cell parameters and the lattice energy for the 5-carboxy[3.3]-orthoparacyclophane (**1**) are shown in Table 6. The agreement of the unit cell parameters with those determined by the experiment is good. We are now in the process of evaluating the Gibbs free energy for the MM4 estimated crystal structure. The results will soon be reported elsewhere.

Concluding Remarks

The MM4 force field, whose accuracy with regard to the structure and energy has been developed significantly by adding new MM4 equations (cross terms)[2c] to the original MM3 force field, appears to be accurate enough to predict the conformational equilibrium of the flexible [3.3]- or [4.4]orthoparacyclophane molecules in the gas phase. The electrostatics from the aromatic C−H bond dipole, the improved van der Waals interactions, and torsion−bend cross terms in the MM4 force field are assumed to be essential energetic terms which can be responsible for the better performance of MM4 over the MM3 force field in the conformational analyses on the cyclophanes.

In addition, the MM4 force field evaluated the crystal structures of 5-carboxy[3.3]orthoparacyclophane (**1**) and 6-bromo-[4.4]orthoparacyclophane (**2**) correctly. On the basis of the MM4 calculation results, we can say that the principal factor governing the relative steric orientation of the two benzene rings in the [*m.n*]orthoparacyclophane molecules is the balance between the torsional strain and the van der Waals interactions.

Experimental Section

X-ray Crystallographic Experiment. All data collection measurements were made on a Rigaku AFC7R diffractometer with graphite monochromated Mo Kα radiation, and a rotating anode generator at 296 (1) K. The structure was solved by direct methods[18] and expanded using Fourier techniques.[19] The non-hydrogen atoms were refined anisotropically. All calculations were performed using the teXsan[20] crystallographic software package of the Molecular Structure Corporation.

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